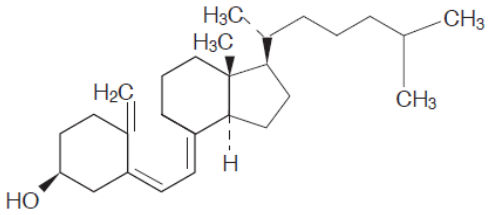
For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

D 360
[Cholecalciferol (Vitamin D_3) Oral Drops]

COMPOSITION
Each ml contains:
Cholecalciferol I.P. (Vitamin D_3) 400 I.U. (As stabilized)
In a flavored syrupy base
Color: Tartrazine

Appropriate overages of vitamins are added to compensate loss on storage.

DESCRIPTION
Cholecalciferol is the naturally occurring form of vitamin D. It is produced from 7-dehydrocholesterol, a sterol present in mammalian skin, by ultraviolet irradiation. The chemical name of cholecalciferol is (5*Z*,7*E*)-(3*S*)-9,10-secocholesta -5,7,10(19)-triene-3-ol. The empirical formula of cholecalciferol is $C_{27}H_{44}O$ and its molecular weight is 384.6. The structural formula is:



CLINICAL PHARMACOLOGY
PHARMACODYNAMIC
The *in vivo* synthesis of the major biologically active metabolites of vitamin D occurs in two steps. The first hydroxylation takes place in the liver (to 25-hydroxy vitamin D) and the second in the kidneys (to 1, 25-dihydroxy- vitamin D). Vitamin D metabolites promote the active absorption of calcium and phosphorus by the small intestine, thus elevating serum calcium and phosphate levels sufficiently to permit bone mineralization. Vitamin D metabolites also mobilize calcium and phosphate from bone and probably increase the reabsorption of calcium and perhaps also of phosphate by the renal tubules. There is a time lag of 10 to 24 hours between the administration of vitamin D and the initiation of its action in the body due to the necessity of synthesis of the active metabolites in the liver and kidneys. Parathyroid hormone is responsible for the regulation of this metabolism in the kidneys.

PHARMACOKINETICS
Vitamin D substances are well absorbed from the gastrointestinal tract. The presence of bile is essential for adequate intestinal absorption; absorption may be decreased in patients with decreased fat absorption.

Vitamin D and its metabolites circulate in the blood bound to a specific α-globulin. Vitamin D can be stored in adipose and muscle tissue for long periods of time. It is slowly released from such storage sites and from the skin where it is formed in the presence of sunlight or ultraviolet light. Cholecalciferol have a slow onset and a long duration of action; calcitriol and its analogue alfacalcidol, however, have a more rapid action and shorter half-lives. Cholecalciferol is hydroxylated in the liver by the enzyme vitamin D 25 - hydroxylase to form 25-hydroxycholecalciferol (calcifediol). These compounds undergo further hydroxylation in the kidneys by the enzyme vitamin D 1-hydroxylase to form the active metabolites 1, 25-dihydroxycholecalciferol (calcitriol).
Further metabolism also occurs in the kidneys, including the formation of the 1,24,25-trihydroxy derivatives. Vitamin D compounds and their metabolites are excreted mainly in the bile and faeces with only small amounts appearing in urine; there is some enterohepatic recycling but it is considered to have a negligible contribution to vitamin D status. Certain vitamin D substances may be distributed into breast milk.

INDICATIONS

For the treatment of vitamin D deficiency in:

- Hypophosphataemic rickets and osteomalacia
- Postgastrectomy and intestinal malabsorption osteomalacia
- Osteomalacia associated with prolonged use of anticonvulsants and other hepatic microsomal enzyme-inducing drugs
- Osteomalacia associated with hepatobiliary disorders

As an adjuvant in the management of chronic disease state in which vitamin D deficiency is Suspected such as CVD, Diabetes, Cancer (breast, prostate and colon), infectious diseases, TB and COPD.

DOSAGE AND ADMINISTRATION

A minimum dietary intake of 400 IU/day (10 mcg/day) for neonates, children, and adolescents. If this amount cannot be achieved through their normal diet, a vitamin D supplement should be administered. Exclusively breastfed infants and those consuming less than 1 L of infant formula/day should receive 400 IU/day of an oral liquid vitamin D product. Preterm infants should receive 400 to 800 IU of vitamin D (10 to 20 mcg) per day to compensate for decreased placental transfer in utero and decreased gastrointestinal absorption after birth.

For treatment of documented vitamin D deficiency, infants may be given 1,000 to 2,000 International Units/day (25 to 50 mcg) and older children may be given up to 5,000 IU/day (125 mcg) for 2 to 3 months. A high-dose short-course regimen providing a total of 100,000 to 600,000 IU (2.5 to 15 mg) over 1 to 5 days has been suggested for patients who might not adhere to longer regimens.

Vitamin D dosing in children with kidney disease or other chronic illnesses should be based on serum 25(OH)D levels. Table 1 provides general recommendations for these

patients. Table 2 lists dosing recommendations for children with severe or chronic deficiency states

Table 1: Examples of Vitamin D Dosing Based on Serum 25(OH)D Levels

25(OH)D	Dose
16-30 ng/mL	2,000 IU/day (50 mcg) or 50,000 IU (1.25 mg) monthly for 3 months
5-15 ng/mL	4,000 IU/day (100 mcg) or 50,000 IU (1.25 mg) every other week for 3 months
< 5 ng/mL	8,000 IU/day (200 mcg) or 50,000 IU(1.25 mg) weekly for 1 month followed by 4,000 IU/day or 50,000 IU every other week for a total of 3 months

Table 2: Examples of Vitamin D Dosing Based on Diagnosis

Diagnosis	Dose
Rickets	1,000-10,000 IU/day (25 to 250 mcg/day) for 2 to 3 months, followed by maintenance treatment with 400 to 1,000 IU/day
Malabsorption	25,000 IU/day syndromes (625 mcg/day)
Familial hypophosphatemia	40,000-80,000 IU/day (1 to 2 mg/day)
Hypopara thyroidism	200,000 IU/day (5 mg/day), titrated to maintain optimal levels

Vitamin D supplements may be taken with or without food. Administration with food may be useful to reduce stomach upset. Calcium supplementation (30 to 75 mg/kg/day oral elemental calcium) is often necessary to maximize response in patients with vitamin D deficiency. Patients receiving vitamin D supplementation beyond the recommended daily dietary intake should undergo periodic monitoring of serum 25(OH)D levels, using an assay for both 25(OH)D2 and 25(OH)D3, as well as serum calcium, phosphorus, and alkaline phosphatase at one and three months or until stabilized, followed by annual reassessment. Parathyroid and bone mineralization studies should be conducted as needed.

CONTRAINDICATIONS

This formulation contraindicated in the patient known to be hypersensitive (allergic) to Vitamin D used in this formulation. In patients with hypercalcemia, malabsorption syndrome, abnormal sensitivity to the toxic effects of vitamin D, and hypervitaminosis D.

WARNING

Hypersensitivity to vitamin D may be one etiologic factor in infants with idiopathic hypercalcemia. In these cases vitamin D must be strictly restricted.

PRECAUTIONS

Vitamin D should not be given to patients with hypercalcaemia. It should be used with caution in infants, who may have increased sensitivity to its effects, and patients with renal impairment or calculi, or heart disease, who might be at increased risk of organ damage if hypercalcaemia occurred. Plasma phosphate concentrations should be controlled during vitamin D therapy to reduce the risk of ectopic calcification. It is advised that patients receiving pharmacological doses of vitamin D should have their plasma-calcium concentration monitored at regular intervals, especially initially or if symptoms suggest toxicity. Similar monitoring is recommended in infants if they are breast fed by mothers receiving pharmacological doses of vitamin D.

Pregnancy

Hypercalcaemia during pregnancy may produce congenital disorders in the offspring, and neonatal hypoparathyroidism. However, the risks to the fetus of untreated maternal hypoparathyroidism are considered greater than the risks of hypercalcaemia due to vitamin D therapy.

Breast feeding

Vitamin D is distributed into breast milk, and its concentration appears to correlate with the amount of vitamin D in the serum of exclusively breast-fed infants. The infant be closely monitored for hypercalcaemia or clinical manifestations of vitamin D toxicity if the mother is taking pharmacological doses of vitamin D.

DRUG INTERACTIONS

There is an increased risk of hypercalcaemia if vitamin D is given with thiazide diuretics, calcium, or phosphate. Plasma-calcium concentrations should be monitored in such situations. Some antiepileptics may increase vitamin D requirements (e.g. carbamazepine, phenobarbital, phenytoin, and primidone). Rifampicin and isoniazid may reduce the effectiveness of vitamin D. Corticosteroids may counteract the effect of vitamin D.

Ketoconazole may inhibit the metabolism of paricalcitol and these drugs should be used with caution together; care should be taken when using paricalcitol with other potent inhibitors of the cytochrome P450 isoenzyme CYP3A4. Mineral oil interferes with the absorption of fat-soluble vitamins, including vitamin D preparations.

ADVERSE EFFECTS

Excessive intake of vitamin D leads to the development of hyperphosphataemia or hypercalcaemia. Associated effects of hypercalcaemia include hypercalciuria, ectopic calcification, and renal and cardiovascular damage. Symptoms of overdosage include anorexia, lassitude, nausea and vomiting, constipation or diarrhoea, polyuria, nocturia, sweating, headache, thirst, somnolence, and vertigo. Interindividual tolerance to vitamin D varies considerably; infants and children are generally more susceptible to its toxic effects. The vitamin should be withdrawn if toxicity occurs. It has been stated that vitamin D dietary supplementation may be detrimental in persons already receiving an

adequate intake through diet and exposure to sunlight, since the difference between therapeutic and toxic concentrations is relatively small.

The most potent forms of vitamin D, such as alfacalcidol and calcitriol, might reasonably be expected to pose a greater risk of toxicity; however, their effects are reversed rapidly on withdrawal. Hypersensitivity reactions have occurred. Skin irritation or contact dermatitis has been reported with topical preparations.

Hypercalcaemia: Vitamin D is the most likely of all vitamins to cause overt toxicity. Doses of 60000 units daily can cause hypercalcaemia, with muscle weakness, apathy, headache, anorexia, nausea and vomiting, bone pain, ectopic calcification, proteinuria, hypertension, and cardiac arrhythmias. Chronic hypercalcaemia can lead to generalised vascular calcification, nephrocalcinosis, and rapid deterioration of renal function. Hypercalcaemia has been reported in a patient after brief industrial exposure to colecalciferol.

A study in children treated for renal osteodystrophy has provided some evidence that hypercalcaemia may occur more frequently with calcitriol than with ergocalciferol. Another such study has suggested that vitamin D has nephrotoxic properties independent of the degree of induced hypercalcaemia, and that the decline in renal function may be more marked with calcitriol. Topical calcitriol may affect calcium homoeostasis, and hypercalcaemia has been reported in some studies. Hypervitaminosis D is characterized by effects on the following organ system:

Renal: Impairment of renal function with polyuria, nocturia, polydipsia, hypercalciuria, reversible azotemia, hypertension, nephrocalcinosis, generalized vascular calcification, or irreversible renal insufficiency which may result in death.

CNS: Mental retardation.

Soft Tissues: Widespread calcification of the soft tissues, including the heart, blood vessels, renal tubules, and lungs.

Skeletal: Bone demineralization (osteoporosis) in adults occurs concomitantly. Decline in the average rate of linear growth and increased mineralization of bones in infants and children (dwarfism), vague aches, stiffness, and weakness.

Gastrointestinal: Nausea, anorexia, constipation.

Metabolic: Mild acidosis, anemia, weight loss.

OVERDOSAGE

The effects of administered vitamin D can persist for two or more months after cessation of treatment.

Hypervitaminosis D is characterized by:
Hypercalcemia with anorexia, nausea, weakness, weight loss, vague aches and stiffness, constipation, mental retardation, anemia, and mild acidosis.

Impairment of renal function with polyuria, nocturia, polydipsia, hypercalciuria, reversible azotemia, hypertension, nephrocalcinosis, generalized vascular calcification, or irreversible renal insufficiency which may result in death. Widespread calcification of the soft tissues, including the heart, blood vessels, renal tubules, and lungs. Bone demineralization (osteoporosis) in adults occurs concomitantly. Decline in the average rate of linear growth and increased mineralization of bones in infants and children (dwarfism).

The treatment of hypervitaminosis D with hypercalcemia consists of immediate withdrawal of the vitamin, a low calcium diet, generous intake of fluids, along with symptomatic and supportive treatment. Hypercalcemic crisis with dehydration, stupor, coma, and azotemia requires more vigorous treatment. The first step should be hydration of the patient. Intravenous saline may quickly and significantly increase urinary calcium excretion. A loop diuretic (furosemide or ethacrynic acid) may be given with the saline infusion to further increase renal calcium excretion. Other reported therapeutic measures include dialysis or the administration of citrates, sulfates, phosphates, corticosteroids, EDTA (ethylenediaminetetraacetic acid), and mithramycin via appropriate regimens. With appropriate therapy, recovery is the usual outcome when no permanent damage has occurred. Deaths via renal or cardiovascular failure have been reported.

DIRECTION FOR USE:
Use calibrated dropper provided in the pack. Pull out the teat slightly to facilitate administration.

Shake well before use
For Pediatric use only

EXPIRY DATE
Do not use later than date of expiry.

STORAGE
Store below 30^{o}C, in a cool and dry place. Protect from light.

PRESENTATION
D 360 oral drops are available in 15ml Bottle.

MARKETED BY:
torrent PHARMA

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